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PHARMACEUTICAL COMPOSITION WITH IMPROVED ABSORPTION

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(54) Title of the Invention

Pharmaceutical composition with improved absorption

(57) Abstract

Object

To put forward a pharmaceutical composition with improved absorption.

Means of Resolution

A pharmaceutical composition which is formed by dissolving 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium and a polymer in ethanol or a mixed solvent of water/ethanol, then distilling off the solvent; and a pharmaceutical composition which is formed by shaping 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium and a polymer with a stirred compression type granulator.

Patent Claims

[Claim 1]

A pharmaceutical composition which is formed by dissolving 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium and a macromolecule in ethanol or a mixed solvent of water/ethanol, then distilling off the solvent.

[Claim 2]

A pharmaceutical composition which is formed by shaping 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium and a macromolecule with a stirred compression type granulator.

[Claim 3]

A pharmaceutical composition in accordance with Claim 1 or 2, wherein the macromolecule is hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose, carboxymethyl ethyl cellulose, methyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone or methacrylic acid – acrylic acid copolymer.

Detailed Description of the Invention

(0001)

Technical Sphere of the Invention

The inventions relates to a solid dispersion of 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium.

(0002)

Technology of the Prior Art

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium (in the following, abbreviated to 'the compound used in the invention') is a therapeutic in development as a drug for treating chronic heart failure and pulmonary hypertension. However, the compound used in the invention has a very low solubility in a wide pH range, and so it is not absorbed sufficiently from the digestive tract, and absorption is irregular. However, methods to improve absorption of sparingly soluble pharmaceuticals are known, such as finely dividing the drug, forming a solvate, increasing the surface area by solid surface adsorption, forming polycrystals, grinding with excipients and forming solid dispersions.

(0003)

Problem to be Solved by this Invention

Because 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium is highly reactive with excipients commonly used for manufacturing drug formulations, it is readily converted from the sodium salt into the free form which has decreased solubility. However, it is not possible to obtain a sufficient effect of increasing the solubility by finely dividing and so on, to increase the solubility and improve the absorption, because the conversion to the free form also increases when the surface area increases. The inventors studied to resolve these problems with the result that the problems can be resolved by the methods shown below

(0004)

Form for Carrying Out the Invention

The invention is a pharmaceutical composition which is formed by dissolving 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium and a polymer in ethanol or a mixed solvent of water/ethanol, then distilling off the solvent. Moreover the invention is a pharmaceutical composition which is formed by shaping 2-(4-

carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium and a polymer with a stirred compression type granulator.

(0005)

In the invention 'macromolecule' means a polymer or macromolecule which dissolves or disperses in water. It also includes the case when it is insoluble at low pH when dissolved or dispersed in water, but dissolves or disperses at high pH, specifically it means is hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose, carboxymethyl ethyl cellulose, methyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone or methacrylic acid – acrylic acid copolymer, and hydroxypropyl cellulose acetate phthalate, carboxymethyl ethyl cellulose are nominated as preferred materials.

(0006)

The mixing ratio of the water/ethanol mixed solvent is not limited particularly, but a mixing ratio wherein the compound used in the invention and the macromolecule dissolve together is preferred. Normally it is water 1-90%, ethanol 99-10%, more preferably water 1-30 %, ethanol 99-70 %. Normally, the dissolution of the compound used in the invention and the macromolecule is performed at room temperature, but if necessary it may be performed under cooling or heating.

(0007)

Moreover, in the invention, the stirred compression type granulator is a mechanism which performs granulation by stirring and mixing the compound used in the invention and the water-soluble macromolecule, for example by blades provided inside the granulator, while applying pressure to extrude, for example from a screen or nozzles, to extrude granules, and a mechanism such as a biaxial extruder can be used. In the invention, the compound used in the invention is considered to form a solid dispersion in the pharmaceutical composition. The solid dispersion is a form where the compound used in the invention is dispersed in the macromolecule as medium, and the form where it is dispersed in molecular form or in non-crystalline form are preferred, but it is not limited to these dispersion forms, and it may also be dispersed in crystalline form, for example.

(0008)

The production method of 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium, which is the compound used in the invention, is based on the

method disclosed for example in WO93/07124. A mixture of 2,4,6-trichloroquinazoline 3.6g, piperonylamine 2.4g, triethylamine 1.6g and isopropyl alcohol 50 ml was heated and refluxed for 1.5 hours. While hot, the precipitate was filtered off, and 2,6-dichloro-4-(3,4-methylenedioxybenzyl)aminoquinazoline 5.2g was obtained.

(0009)

Subsequently, methyl isonipecotate 3.61 g, triethylamine 2.32g and 2-propanol 5 ml were added to 2,6-dichloro-4-(3,4-methylenedioxybenzyl)aminoquinazoline 1g, and the mixture was refluxed for 100 minutes. It was extracted twice with chloroform, the combined organic layers were washed with water, then dried with magnesium sulphate. The solvent was distilled off, then the residue was recrystallized from ethanol-water and 2-(4-ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)amineo-6-chloroquinazoline 1.31g was obtained. Ethanol 10 ml, water 5 ml and sodium hydroxide 820 mg were added to 2-(4-ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline 1g, and the mixture was refluxed for 20 minutes. After concentrating the solvent at reduced pressure, it was neutralised by adding 1H hydrochloric acid, the precipitated crystals were filtered off and 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline 920 mg was obtained. 1N aqueous sodium hydroxide 12 ml and water 40 ml were added to this compound, and it was dissolved by heating, then it was dried in the presence of phosphorus pentoxide and 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium was obtained.

(0010)

In the invention, the mixing ratio of 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium and the water-soluble macromolecule is at least one weight part of water-soluble macromolecule, preferably at least 4 weight parts, to 1 weight part of 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium. In the invention, the method of manufacturing the solid dispersion, it can be obtained for example by dissolving the compound used in the invention and hydroxypropylcellulose acetate phthalate in 85% ethanol/water mixed solvent, then evaporating the solvent to dryness. The obtained solid dispersion can be pulverised, sieved, mixed with other materials as necessary to produce granules, tablets and so on.

(0011)

Effect

By making the solid dispersion according to the invention, the solubility of the compound used in the invention becomes much higher than the solubility of the original crystalline material by modifying the crystal structure without decomposition. The compound used in the invention can show the effect of higher absorption from the digestive tract.

(0012)

Examples

The invention is shown in more detail in the following examples, but the invention is not limited to these.

Example 1

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium 1g was mixed with hydroxypropylcellulose acetate phthalate 5g, and mixed with a mixed solvent of 85% ethanol/water, then the solvent was evaporated to dryness and a composition in accordance with the invention was produced.

Example 2

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium 2g was mixed with polyvinylpyrrolidone 10g, and dissolved in ethanol, then the solvent was evaporated to dryness and a composition in accordance with the invention was produced.

(0013)

Example 3

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium 200g was mixed with hydroxypropylcellulose acetate phthalate 100g, and processed in an extruder to produce a composition in accordance with the invention. This composition was pulverized in a jet mill and classified, to produce a granulate.

Example 4

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium 2g was mixed with hydroxypropyl methyl cellulose 10g, dissolved in a mixed solvent of 85% ethanol/water, the solvent was evaporated to dryness and a composition in accordance with the invention was produced.

(0014)

Example 5

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium 200g was mixed with hydroxypropyl methyl cellulose 1000g, processed in an extruder, and a composition according to the invention was produced, then it was pulverized in a hammer mill and classified, and a granulate was produced.

Example 6

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium 200g was mixed with polyvinyl pyrrolidone (PVP K-30) 1000g, and dissolved by heating at 120 °C, then cooled and pulverized and a composition in accordance with the invention was produced.

(0015)

Effect

Elution of the compound used in the invention into Japanese Pharmacopoeia liquid 2 900ml at 37°C was measured using the paddle method with rotation rate 100rpm, using a composition obtained by mixing hydroxypropylcellulose acetate phthalate, hydroxypropyl methyl cellulose, carboxymethyl ethyl cellulose or polyvinyl pyrrolidone 5 weight parts to the compound used in the invention 1 weight part, dissolving ethanol/water mixed solvent and removing the solvent. The results are shown in Figure 1. As a control, the compound used in the invention only was used. The solubility was higher and the dissolution was faster for all the compositions according to the invention than for the control.

(0016)

Elution of the compound used in the invention into Japanese Pharmacopoeia liquid 2 (37°C, 900 ml, paddle method, 100 rpm) was measured, using a composition obtained by mixing hydroxypropylcellulose acetate phthalate 1 to 5 weight parts to the compound used in the invention 1 weight part, dissolving ethanol/water mixed solvent and removing the solvent. The results are shown in Figure 2. The solubility was higher and the dissolution was faster for all the compositions according to the invention than for the compound used in the invention alone, in particular, great solubility and improved dissolution rate were recognised when the mixing ratio was 4 weight parts or more.

(0017)

Elution of the compound used in the invention into Japanese Pharmacopoeia liquid 2 (37°C, 900 ml, paddle method, 100 rpm), using a composition obtained by mixing hydroxypropylcellulose acetate phthalate 3 to 5 weight parts to the compound used in the invention 1 weight part, and extruding. The results are shown in Figure 3. Great solubility and improved dissolution rate were recognised at all of the mixing ratios.

(0018)

2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium 15 mg was administered orally to beagle dogs, using the solid dispersion obtained in example 3. The concentration change of drug in blood following the administration is shown in Figure 4. In the test, tablets produced by normal methods from crystals of the compound used in the invention which were not in the form of solid dispersion were used, and the crossover method was performed. As is clear from Figure 4, the quantity absorbed from the solid dispersion in accordance with the invention and the scatter of the absorption are greatly improved compared with the control.

(0019)

2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium 15 mg was administered orally to beagle dogs, using the solid dispersion obtained in example 2. The concentration change of drug in blood following the administration is shown in Figure 4. In the test, tablets produced by normal methods from crystals of the compound used in the invention which were not in the form of solid dispersion were used, and the crossover method was performed. As is clear from Figure 5, the quantity absorbed from the solid dispersion in accordance with the invention and the scatter of the absorption are greatly improved compared with the control.

(0020)

Explanation of the Figures

Figure 1

Figure 1 shows the elution of the compound used in the invention when it was dispersed in each of the macromolecules.

Figure 2

Figure 2 shows the elution of the compound used in the invention when it was dispersed in hydroxypropylmethylcellulose phthalate in various proportions

Figure 3

Figure 3 shows the elution of the compound used in the invention from a composition obtained by dispersing it in hydroxypropylmethylcellulose phthalate in various proportions, and extruding.

Figure 4

Figure 4 shows the change in blood concentration of the compound used in the invention when it was administered to beagle dogs as a composition of the compound and hydroxypropylmethylcellulose phthalate.

Figure 5

Figure 5 shows the change in blood concentration of the compound used in the invention when it was administered to beagle dogs as a composition of the compound and polyvinyl pyrrolidone.

Figure 1

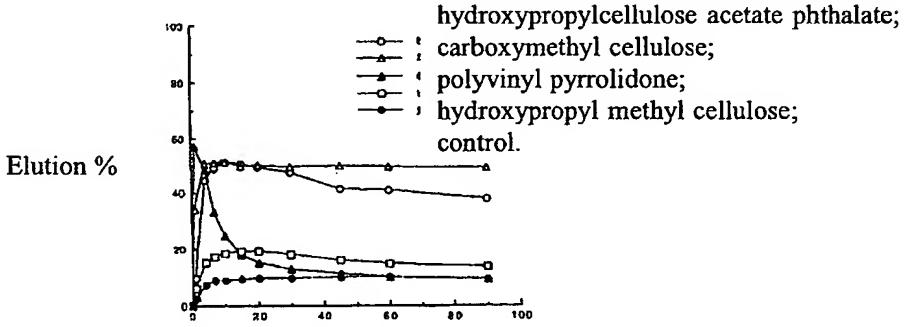


Figure 2

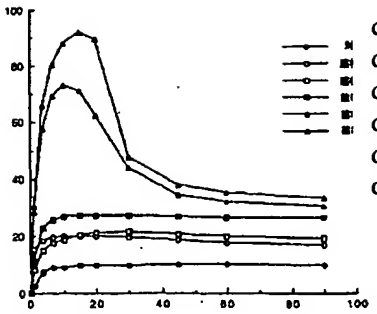


Figure 3

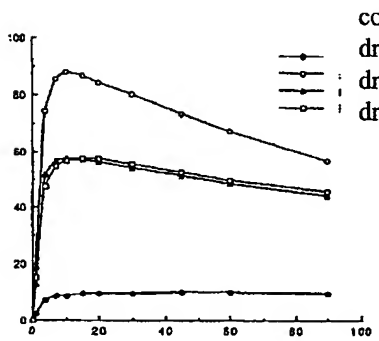


Figure 4

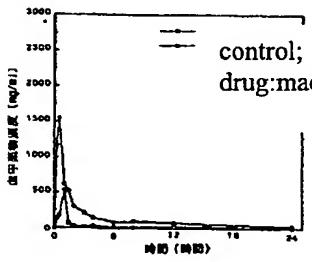
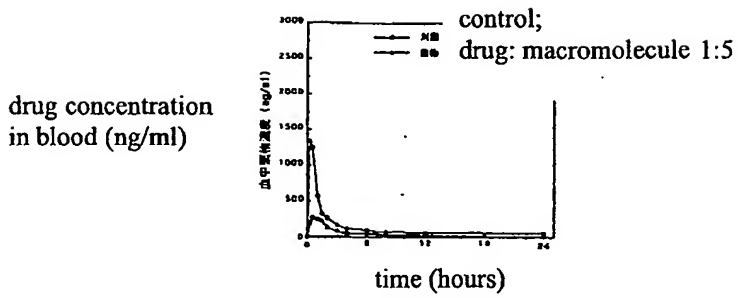


Figure 5



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